(FILE 'HOME' ENTERED AT 13:11:48 ON 20 SEP 1999)

FILE 'MEDLINE, CAPLUS, EMBASE, BIOSIS' ENTERED AT 13:12:00 ON 20 SEP 1999

L1 3650 S (D IMMITIS) OR (DIROFILARIA IMMITIS)
L2 6 S L1 AND (METALLOPROTEASE OR METALLOENDOPEPTIDASE)
L3 4 DUP REM L2 (2 DUPLICATES REMOVED)
L4 10 S L1 AND ZINC
L5 1 S L1 AND ASTACIN

(FILE 'USPAT' ENTERED AT 13:21:25 ON 20 SEP 1999)
L1 116 S (D IMMITIS) OR (DIROFILARIA IMMITIS)
L2 28 S L1 AND PROTEASE
L3 7 S L1 AND (METALLOPROTEASE OR METALLOENDOPEPTIDASE)

=> d bib ab clm l3 1-7

US PAT NO: 5,912,337 [IMAGE AVAILABLE] L3: 1 of 7
DATE ISSUED: Jun. 15, 1999
TITLE: Parasitic helminth p22U proteins
INVENTOR: Cynthia Ann Tripp, Ft. Collins, CO
Glenn Robert Frank, Ft. Collins, CO
Robert B. Grieve, Ft. Collins, CO
ASSIGNEE: Heska Corporation, Ft. Collins, CO (U.S. corp.)
Colorado State University Research Foundation, Ft. Collins, CO (U.S. corp.)
APPL-NO: 08/460,428
DATE FILED: Jun. 2, 1995
ART-UNIT: 161
PRIM-EXMR: James C. Housel
ASST-EXMR: Rodney P. Swartz
LEGAL-REP: Sheridan Ross P.C.

US PAT NO: 5,912,337 [IMAGE AVAILABLE] L3: 1 of 7

ABSTRACT:
The present invention relates to an isolated protein comprising a filariid p22U protein. In a preferred embodiment, the filariid p22U protein selectively binds to immune serum which is derived from an animal that is immune to infection by **Dirofilaria immitis**. Such an animal can be immunized with a composition comprising third and/or fourth stage **Dirofilaria immitis** larvae. In a preferred embodiment, the filariid p22U protein is a Dirofilaria protein.

CLAIMS:

CLMS(1)

What is claimed is:

1. An isolated filariid p22U protein, comprising an amino acid sequence selected from the group consisting of:
(a) SEQ ID NO:4; and,
(b) a fragment of SEQ ID NO:4 that elicits an IgG response.

CLMS(2)

2. The protein of claim 1, wherein said protein selectively binds to immune serum derived from an animal that is immune to infection by **Dirofilaria immitis**.

CLMS(3)

3. The protein of claim 2, wherein said immune serum is derived from an animal immunized with a composition comprising **Dirofilaria**

immitis larvae selected from the group consisting of third stage larvae, fourth stage larvae, and mixtures of third stage and fourth stage larvae.

CLMS(4)

4. The protein of claim 1, wherein said filariid is selected from a group consisting of Dirofilaria, Onchocerca, Brugia, Wuchereria, Loa, Acanthocheilonema, Setaria, Parafilaria, and Stephanofilaria filarial nematodes.

CLMS(5)

5. The protein of claim 1, wherein said filariid comprises a **Dirofilaria immitis** nematode.

CLMS(6)

6. The protein of claim 1, wherein said protein is encoded by a nucleic acid sequence comprising SEQ ID NO:3.

CLMS(7)

7. The protein of claim 1, wherein said protein, when administered to an animal elicits an immune response against said protein.

CLMS(8)

8. A method to determine infection of an animal by a filariid, said method comprising:
(a) contacting serum collected from an animal with the isolated filariid p22U protein of claim 1, wherein selective binding of an antibody from said serum to said isolated filariid p22U protein forms a selective binding complex; and
(b) determining the presence of said complex, wherein the presence of said complex indicates that said animal is infected by said filariid.

CLMS(9)

9. The method of claim 8, wherein said method is used to detect heartworm infections in said animal.

US PAT NO: 5,863,775 [IMAGE AVAILABLE] L3: 2 of 7
DATE ISSUED: Jan. 26, 1999
TITLE: Control of parasites
INVENTOR: Howard John Atkinson, Leeds, Great Britain
Vas Michael Koritsas, Leeds, Great Britain
Donald Lewis Lee, Leeds, Great Britain
Andrew Neilson MacGregor, Canterbury, Great Britain
Judith Elizabeth Smith, Leeds, Great Britain
ASSIGNEE: The University of Leeds, Leeds, England (foreign corp.)
APPL-NO: 08/702,682
DATE FILED: Dec. 20, 1996
ART-UNIT: 191
PRIM-EXMR: Nancy Degen
LEGAL-REP: William A. Barrett, Steven J. Hultquist

US PAT NO: 5,863,775 [IMAGE AVAILABLE] L3: 2 of 7

ABSTRACT:

The invention relates to a method of combating an animal parasite in a host which comprises delivering an anti-parasitic protein to the parasite or to a locus thereof by administering the protein to the host animal as

a medicament or as a food. The anti-parasitic protein may be an inhibitor of an enzyme of the parasite, for example an inhibitor of a digestive enzyme such as a cysteine protease inhibitor. The parasite may be a helminth or a protozoan, for example, a nematode. According to one embodiment the anti-parasitic protein is expressed in a transgenic plant which may be a dietary crop for the host animal.

CLAIMS:

CLMS(1)

We claim:

1. A method for combating an infection by an animal parasite in a host animal which comprises delivering an anti-parasitic protein to the parasite or a locus thereof by administering the protein to the host animal as a medicament or as a food wherein the antiparasitic protein exhibits an anti-parasitic action which does not involve the immune system of the host and wherein said anti-parasitic protein is an enzyme of said parasite.

CLMS(2)

2. A method according to claim 1 wherein said animal parasite is selected from the group consisting of helminths and protozoans.

CLMS(3)

3. A method according to claim 2 wherein said animal parasite is a nematode.

CLMS(4)

4. A method according to claim 1 wherein said anti-parasitic protein is an inhibitor of a digestive enzyme of said parasite.

CLMS(5)

5. A method according to claim 4 wherein said anti-parasitic protein is a cysteine protease inhibitor.

CLMS(6)

6. A method according to claim 4 wherein said anti-parasitic protein is a cysteine protease inhibitor from maize or rice.

CLMS(7)

7. A method according to claim 1 wherein said anti-parasitic protein is expressed by a transgenic plant.

CLMS(8)

8. A method according to claim 7 wherein said transgenic plant is a dietary crop for said host animal.

CLMS(9)

9. A composition adapted for oral, parenteral or topical administration to a host animal, which composition combats a parasitic infection by an animal parasite to which said host animal is subject, which composition comprises an anti-parasitic protein directed against said animal parasite, said anti-parasitic protein having been expressed by a transgenic plant, wherein said anti-parasitic protein is a cysteine protease inhibitor from maize or rice.

CLMS(10)

10. A composition according to claim 9 wherein said transgenic plant is a dietary crop for said host animal.

CLMS(11)

11. A composition according to claim 10 wherein said anti-parasitic protein is incorporated into the composition in the form of parts of the transgenic plant.

CLMS(12)

12. A composition according to claim 10 wherein said animal parasite is selected from the group consisting of helminths and protozoans.

CLMS(13)

13. A composition according to claim 12 wherein said animal parasite is a nematode.

CLMS(14)

14. A composition according to claim 9 wherein said anti-parasitic protein is extracted from the transgenic plant prior to incorporation into the composition.

CLMS(15)

15. A composition according to claim 9 in a form adapted for oral administration.

CLMS(16)

16. A composition according to claim 15 in the form of a food or a medicament for said host animal.

CLMS(17)

17. A process for the manufacture of a composition adapted for administration to a host animal as a medicament or a food and which combats an infection by an animal parasite to which said host animal is subject, which process comprises processing a transgenic plant into a medicament or a food for said host animal, said transgenic plant being transformed with DNA encoding an anti-parasitic protein against said animal parasite and expressing said protein within the transgenic plant, wherein said anti-parasitic protein is an inhibitor of an enzyme of said parasite.

CLMS(18)

18. A process according to claim 17 wherein said animal parasite is selected from the group consisting of helminths and protozoans.

CLMS(19)

19. A process according to claim 17 wherein said animal parasite is a nematode.

CLMS(20)

20. A process according to claim 18 wherein said anti-parasitic protein is an inhibitor of a digestive enzyme of said parasite.

CLMS(21)

21. A process according to claim 20 wherein said anti-parasitic protein is a cysteine protease inhibitor.

CLMS(22)

22. A process according to claim 21 wherein said anti-parasitic protein is a cysteine protease inhibitor from maize or rice.

CLMS(23)

23. A process according to claim 17 wherein said transgenic plant is a dietary crop for said host animal.

CLMS(24)

24. A transgenic plant transformed with a DNA encoding for a cysteine protease inhibitor from maize or rice wherein the plant, when ingested by a host animal infected by a parasite producing a protease, delivers to the parasite a cysteine protease inhibitor in an amount and form which is effective to inhibit the activity of the parasite originated protease and wherein the plant is a dietary crop for the host animal.

CLMS(25)

25. A method for combating an infection by an animal parasite in a host animal which comprises delivering an anti-parasitic protein to the parasite or a locus thereof by administering the protein to the host animal as a medicament or as a food wherein the animal parasite is a helminth or a protozoan, and wherein the antiparasitic protein exhibits an anti-parasitic action which does not involve the immune system of the host and wherein said anti-parasitic protein is an enzyme of said parasite.

CLMS(26)

26. A method for combating an infection by an animal parasite in a host animal which comprises delivering an anti-parasitic protein to the parasite or a locus thereof by administering the protein to the host animal as a medicament or as a food wherein the animal parasite is a nematode, and wherein the antiparasitic protein exhibits an anti-parasitic action which does not involve the immune system of the host and wherein said anti-parasitic protein is an enzyme of said parasite.

US PAT NO: 5,804,200 [IMAGE AVAILABLE] L3: 3 of 7
DATE ISSUED: Sep. 8, 1998
TITLE: Parasitic nematode proteins and vaccines
INVENTOR: Robert B. Grieve, La Porte, CO
Glenn R. Frank, Fort Collins, CO
ASSIGNEE: Colorado State University Research Foundation, Ft. Collins, CO (U.S. corp.)
Heska Corporation, Ft. Collins, CO (U.S. corp.)
APPL-NO: 08/408,120
DATE FILED: Mar. 20, 1995
ART-UNIT: 182
PRIM-EXMR: Hazel F. Sidberry
LEGAL-REP: Sheridan Ross P.C.

US PAT NO: 5,804,200 [IMAGE AVAILABLE] L3: 3 of 7

ABSTRACT:
Immunogens derived from proteins isolatable from the L3 and L4 larval

stages of nematodes parasitic in mammals, and including a protein of about 20.5 kD, are disclosed. The proteins of the invention are identified using biological materials verified to destroy or impair the parasitic nematode in an in vivo incubator. Cells, serum or fractions thereof obtained from immune natural hosts are validated in a method wherein a recoverable implant of the parasitic nematodes is used to assess the protective effect when these materials are provided passively to the animal incubator.

CLAIMS:

CLMS(1)

What is claimed is:

1. An isolated protein isolatable from the L3 or L4 larval stage of **D. immitis**, said protein having amino acid sequence ESQEETVSF EESDEDYEDD SEDQTKEEEH SKEEDRSEEH DDHSAEDDKF VTKGKFVESD GKMKHCKTHE ACYDQREPQS WCILKPHQSW TQRGCFCESK KHACVIERKS GDKLEYSYCS PRKNWQCSYD (SEQ ID NO:27).

US PAT NO: 5,750,391 [IMAGE AVAILABLE] L3: 4 of 7
DATE ISSUED: May 12, 1998
TITLE: Filariid nematode cysteine protease proteins
INVENTOR: Cynthia Ann Tripp, Ft. Collins, CO
Glenn R. Frank, Ft. Collins, CO
Robert B. Grieve, Windsor, CO
ASSIGNEE: Heska Corporation, Ft. Collins, CO (U.S. corp.)
APPL-NO: 08/463,989
DATE FILED: Jun. 5, 1995
ART-UNIT: 184
PRIM-EXMR: Robert A. Wax
ASST-EXMR: Kawai Lau
LEGAL-REP: Sheridan Ross P.C.

US PAT NO: 5,750,391 [IMAGE AVAILABLE] L3: 4 of 7

ABSTRACT:
The present invention relates to parasite astacin **metalloendopeptidase** and filariid cysteine protease proteins, nucleic acid molecules having sequences that encode such proteins, antibodies raised against such proteins and compounds that can inhibit the activities of parasite astacin **metalloendopeptidases** or cysteine proteases. The present invention also includes methods to obtain such nucleic acid molecules, proteins, antibodies and inhibitors. The present invention also includes therapeutic compositions comprising such nucleic acid molecules, proteins, antibodies and inhibitors as well as their use to protect animals from disease caused by parasites, such as heartworm.

CLAIMS:

CLMS(1)

What is claimed is:

1. An isolated protein comprising an adult filariid nematode cathepsin L cysteine protease protein.

CLMS(2)

2. The protein of claim 1, wherein said protein, when administered in an effective manner, elicits an immune response against a filariid cysteine protease.

CLMS(3)

3. The protein of claim 1, wherein said protein has cysteine protease activity.

CLMS(4)

4. The protein of claim 1, wherein said filariid nematode is selected from the group consisting of Dirofilaria, Acanthocheilonema, Brugia, Dipetalonema, Loa, Onchocerca, Parafilaria, Setaria, Stephanofilaria and Wuchereria filariid nematodes.

CLMS(5)

5. The protein of claim 1, wherein said filariid nematode comprises **D. immitis**.

CLMS(6)

6. The protein of claim 1, wherein said protein comprises amino acid sequence SEQ ID NO:13.

CLMS(7)

7. The protein of claim 1, wherein said protein is encoded by a nucleic acid sequence comprising SEQ ID NO:12.

CLMS(8)

8. The protein of claim 1, wherein said protein is produced by a process comprising culturing in an effective medium a recombinant cell transformed with a nucleic acid molecule encoding said protein to produce said protein.

CLMS(9)

9. The protein of claim 1, wherein said protein is used to identify an inhibitor of cysteine protease activity.

US PAT NO: 5,691,186 [IMAGE AVAILABLE] L3: 5 of 7
DATE ISSUED: Nov. 25, 1997
TITLE: Filariid cysteine protease genes
INVENTOR: Cynthia Ann Tripp, Ft. Collins, CO
Glenn R. Frank, Ft. Collins, CO
Robert B. Grieve, Windsor, CO
ASSIGNEE: Heska Corporation, Ft. Collins, CO (U.S. corp.)
APPL-NO: 08/463,262
DATE FILED: Jun. 5, 1995
ART-UNIT: 184
PRIM-EXMR: Robert A. Wax
ASST-EXMR: Kawai Lau
LEGAL-REP: Sheridan Ross P.C.

US PAT NO: 5,691,186 [IMAGE AVAILABLE] L3: 5 of 7

ABSTRACT:
The present invention relates to parasite astacin **metalloendopeptidase** and filariid cysteine protease proteins, nucleic acid molecules having sequences that encode such proteins, antibodies raised against such proteins and compounds that can inhibit the activities of parasite astacin **metalloendopeptidases** or cysteine proteases. The present invention also includes methods to obtain such nucleic acid molecules, proteins, antibodies and inhibitors. The present invention also includes therapeutic compositions comprising such nucleic

acid molecules, proteins, antibodies and inhibitors as well as their use to protect animals from disease caused by parasites, such as heartworm.

CLAIMS:

CLMS(1)

What is claimed is:

1. An isolated nucleic acid molecule having a nucleic acid sequence encoding an adult filariid nematode cathepsin L cysteine protease protein.

CLMS(2)

2. The nucleic acid molecule of claim 1, wherein said filariid nematode is selected from the group consisting of Dirofilaria, Acanthocheilonema, Brugia, Dipetalonema, Loa, Onchocerca, Parafilaria, Setaria, Stephanofilaria and Wuchereria filariid nematodes.

CLMS(3)

3. The nucleic acid sequence of claim 1, wherein said filariid nematode is **D. immitis**.

CLMS(4)

4. The nucleic acid molecule of claim 1, wherein said protein elicits an immune response against a filariid cysteine protease.

CLMS(5)

5. The nucleic acid molecule of claim 1, wherein said protein cleaves peptides having a cysteine protease cleavage site of z-Val-Leu-Arg-AMC.

CLMS(6)

6. The nucleic acid molecule of claim 1, wherein said filariid nematode is a tissue-migrating filariid nematode.

CLMS(7)

7. The nucleic acid molecule of claim 1, wherein said nucleic acid molecule comprises a nucleic acid molecule having a nucleic acid sequence selected from the group consisting of SEQ ID NO:12 and SEQ ID NO:20.

CLMS(8)

8. A recombinant nucleic acid molecule comprising an isolated nucleic acid molecule set forth in claim 1 operatively linked to at least one transcription control sequence.

CLMS(9)

9. A transfected host cell comprising a nucleic acid molecule as set forth in claim 1, said cell expressing said nucleic acid molecule.

CLMS(10)

10. A recombinant virus particle, comprising the recombinant nucleic acid molecule of claim 8.

US PAT NO: 5,686,080 [IMAGE AVAILABLE] L3: 6 of 7
DATE ISSUED: Nov. 11, 1997

TITLE: Parasitic helminth p4 proteins
INVENTOR: Cynthia Ann Tripp, Ft. Collins, CO
Glenn Robert Frank, Ft. Collins, CO
Robert B. Grieve, Ft. Collins, CO
ASSIGNEE: Heska Corporation, Ft. Collins, CO (U.S. corp.)
Colorado State University Research Foundation, Ft. Collins, CO (U.S. corp.)
APPL-NO: 08/459,019
DATE FILED: Jun. 2, 1995
ART-UNIT: 182
PRIM-EXMR: Hazel F. Sidberry
LEGAL-REP: Sheridan Ross P.C.

US PAT NO: 5,686,080 [IMAGE AVAILABLE] L3: 6 of 7

ABSTRACT:
The present invention relates to isolated parasitic helminth nucleic acid sequences capable of hybridizing, under stringent conditions, to at least a portion of **D. immitis** nucleic acid sequence p4 and/or to at least a portion of **D. immitis** nucleic acid sequence p22U; to isolated parasitic helminth proteins that are encoded by such parasitic helminth nucleic acid sequences and that are capable of selectively binding to at least one component of immune serum capable of inhibiting helminth development; and to antibodies raised against such isolated parasitic helminth proteins. The present invention also relates to therapeutic compositions comprising such isolated nucleic acid sequences, proteins and/or antibodies. The present invention also includes methods to produce and use such nucleic acids, proteins, antibodies and therapeutic compositions capable of protecting animals from parasitic helminth infection and, particularly, from heartworm infection.

CLAIMS:

CLMS(1)

What is claimed is:

1. An isolated **Dirofilaria immitis** p4 protein, said protein comprising the amino acid sequence SEQ ID NO:2.

CLMS(2)

2. The protein of claim 1, wherein said protein selectively binds to immune serum derived from an animal that is immune to infection by said **Dirofilaria immitis**.

CLMS(3)

3. The protein of claim 1, wherein said protein is encoded by the nucleic acid sequence comprising SEQ ID NO:1.

CLMS(4)

4. The protein of claim 1, wherein said protein comprises a parasitic helminth LDL receptor-related protein class A cysteine-rich motif.

CLMS(5)

5. The protein of claim 4, wherein said motif comprises SEQ ID NO:5.

US PAT NO: 5,639,876 [IMAGE AVAILABLE] L3: 7 of 7
DATE ISSUED: Jun. 17, 1997
TITLE: Nucleic acid molecules encoding novel parasitic helminth proteins

INVENTOR: Cynthia Ann Tripp, Ft. Collins, CO
Glenn Robert Frank, Ft. Collins, CO
Robert B. Grieve, Ft. Collins, CO
ASSIGNEE: Heska Corporation, Ft. Collins, CO (U.S. corp.)
Colorado State University Research Foundation, Ft. Collins, CO (U.S. corp.)
APPL-NO: 08/109,391
DATE FILED: Aug. 19, 1993
ART-UNIT: 182
PRIM-EXMR: Hazel F. Sidberry
LEGAL-REP: Sheridan Ross P.C.

US PAT NO: 5,639,876 [IMAGE AVAILABLE] L3: 7 of 7

ABSTRACT:
The present invention relates to isolated parasitic helminth nucleic acid sequences capable of hybridizing, under stringent conditions, to at least a portion of **D. immitis** nucleic acid sequence p4 and/or to at least a portion of **D. immitis** nucleic acid sequence p22U; to isolated parasitic helminth proteins that are encoded by such parasitic helminth nucleic acid sequences and that are capable of selectively binding to at least one component of immune serum capable of inhibiting helminth development; and to antibodies raised against such isolated parasitic helminth proteins. The present invention also relates to therapeutic compositions comprising such isolated nucleic acid sequences, proteins and/or antibodies. The present invention also includes methods to produce and use such nucleic acids, proteins, antibodies and therapeutic compositions capable of protecting animals from parasitic helminth infection and, particularly, from heartworm infection.

CLAIMS:

CLMS(1)

What is claimed is:

1. An isolated nucleic acid sequence encoding a **Dirofilaria immitis** p4 protein, said protein comprising amino acid sequence SEQ ID NO:2.

CLMS(2)

2. The isolated nucleic acid sequence of claim 1, wherein said isolated nucleic acid sequence encodes a protein capable of selectively binding to immune serum, said immune serum being capable of inhibiting helminth development.

CLMS(3)

3. The isolated nucleic acid sequence of claim 2, wherein said immune serum is derived from an animal that is immune to infection by said helminth.

CLMS(4)

4. The isolated nucleic acid sequence of claim 2, wherein said immune serum is derived from an animal immunized with a composition comprising parasitic helminth larvae selected from the group consisting of third stage larvae, fourth stage larvae, and mixtures of third stage and fourth stage larvae.

CLMS(5)

5. The isolated nucleic acid sequence of claim 1, wherein said isolated nucleic acid sequence is selected from the group consisting of **D.**

immitis nucleic acid sequence p4 and a nucleic acid sequence including **D. immitis** p4.

CLMS(6)

6. The isolated nucleic acid sequence of claim 1, wherein said isolated nucleic acid sequence is obtained by a method comprising:
(a) culturing a parasitic helminth expression library to promote production of proteins encoded by said library;
(b) contacting said library with immune serum to permit binding of said immune serum to proteins expressed by said library that selectively bind to said immune serum; and
(c) selecting a colony or phage plaque that contains a nucleic acid sequence encoding a protein capable of selectively binding to said immune serum.

CLMS(7)

7. A recombinant molecule comprising at least one isolated nucleic acid sequence set forth in claim 1 operatively linked to at least one transcription control sequence.

CLMS(8)

8. A recombinant cell comprising a cell transformed with an isolated nucleic acid sequence set forth in claim 1 operatively linked to a transcription control sequence.

CLMS(9)

9. A recombinant cell comprising a cell transformed with an isolated nucleic acid sequence set forth in claim 1, said cell being transformed by said sequence in a manner such that said recombinant cell produces a protein encoded by said isolated nucleic acid sequence.

CLMS(10)

10. A method to produce an isolated protein comprising culturing in an effective medium a cell which produces said protein, said protein being encoded by a nucleic acid sequence encoding a **Dirofilaria immitis** p4 protein, said protein comprising amino acid sequence SEQ ID NO:2.

CLMS(11)

11. An isolated **Dirofilaria immitis** nucleic acid sequence p4 (SEQ ID NO:1 or a complement thereof).

CLMS(12)

12. A recombinant molecule comprising a nucleic acid sequence set forth in claim 11 operatively linked to at least one transcription control sequence.

CLMS(13)

13. A recombinant cell comprising a cell transformed with a nucleic acid sequence set forth in claim 11, said cell being transformed by said sequence in a manner such that said recombinant cell produces a protein encoded by said isolated nucleic acid sequence.

CLMS(14)

14. The isolated nucleic acid sequence of claim 1, wherein said nucleic acid sequence comprises SEQ ID NO:1 or a complement thereof.